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GASTRIC SECRETION IN CANCER OF THE STOMACH[1]

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Satisfactory study of the gastric secretions in cancer of the stomach has been difficult because of the presence of the products of stagnation (when pyloric obstruction exists) or of blood, pus or other abnormal elements derived from the growth. Hence, the observer has usually dealt with a mixture of foreign materials which give no idea of what sort of gastric juice, if any, the stomach is actually secreting. We have recently applied methods (1) whereby, after fasting and careful lavage and without the introduction of a test-meal, relatively pure secretions may be obtained. The results of the studies which are herewith reported have yielded information of value in diagnosis and have also given some suggestions as to the underlying pathological changes in the stomach associated with the disease.

GASTRIC SECRETION IN CANCER OF THE STOMACH

Literature

The first demonstration of a diminution of hydrochloric acid in cancer of the stomach has been attributed to Golding Bird by Ewald (2) from whom the quotation has been copied by many subsequent writers. A study of the original report (3), however, leaves one in considerable doubt as to the real state of affairs. The patient had suffered from indigestion and heart-burn for years when as "he had just stepped into his gig on leaving Dr. Bright's house . . . . a sudden sensation of extreme faintness overpowered him and a copious gush of blood rushed from his stomach." During the next five months until his death there was "intense burning pain in the region of the stomach with frequent vomiting of very sour and bitter but colourless fluid, holding in suspension numerous brown flocculi." On one occasion "a quart of acid fluid rushed from his stomach." After death,

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which was evidently precipitated by starvation and dehydration, the autopsy showed that "the stomach was enormously distended, its greater curvature reaching nearly to the pubis. The pyloric orifice was so extremely narrowed that the point of a probe entered it with difficulty; it was completely surrounded by a stricture of scirrhus hardness, and about the size of an orange. . . . . Several ulcerated patches existed on the gastric aspect of this scirrhus mass. No other disease was met with in the chest and abdomen." Specimens of vomitus were examined chemically from time to time and it was noted that the hydrochloric acid per pint of vomited fluid fell from 10.652 grains to 1 grain, although the combined acid rose from 15.228 grains to 22.320 grains. The analyses were made by precipitation with silver nitrate before and after ashing. In view of the story of haematemeses, the vomiting of large amounts of clear, sour fluid and the absence of metastases at autopsy, one wonders whether the case was not really one of pyloric stenosis from old ulcer. Furthermore, no conclusive diminution of gastric function was actually demonstrated.

V. d. Velden (4) was the first observer to make any purposeful studies of gastric secretion in cancer of the stomach. He examined the fluid drawn off in cases of gastrectasis and found that in those patients who had cancer there was never any free HCl. Riegel (5) and others supported these findings, and until the appearance of Miehe's thesis in 1890 it was generally agreed that acid was invariably lacking, although it was recognized that anacidity occurred in other conditions as well. Miehe (6) disagreed with the claims of V. d. Velden and of Riegel on the basis of five cases of cancer of the stomach with autopsy in which free HCl had been demonstrated by color reactions after an Ewald meal. Miehe agreed, however, that HCl was usually absent and practically always diminished. Ewald (7) felt that the absence of free HCl was practically constant except in very small early cancers and in cancer on an ulcer basis. Oppeler's studies (8) were among the most thorough of the earlier ones. He states that with intact motor function of the stomach (*i.e.*, with no pyloric obstruction) acid is usually absent, whereas with disturbance of motor function (*i.e.*, with early pyloric cancer) acid is present in strong concentration (*stark vorhanden*). He found no acid with any

advanced ulcerated growth. Einhorn (9) in general supports the previous views but states that acid is sometimes present in greater than normal amount. No actual cases are cited. Riegel (10) later departed from his earlier opinion that acid is invariably absent and admitted that it might be present in very early cases. He states that the acid may diminish during the course of the disease from normal to zero but gives no concrete figures. Cohnheim (11), Hayem and Lion (12), and Boas (13) agreed essentially with the writers just cited. Boas found anacidity in 77.5 per cent of his cases. Smithies and Ochsner (14) report values for free acid varying from 0 to 73, and Hartman (15) in a series of 551 cases, none of which were believed to have followed ulcer, found anacidity in 53.7 per cent, hypoacidity in 15.7 per cent, normal values in 17.4 per cent, and hyperacidity in 4.5 per cent. Brown (16), recently, states that in more than 75 per cent of the cases free HCl is absent.

In summary, then, all observers agree as to the frequency of anacidity in cancer of the stomach, although they find acid present—usually diminished—in a certain percentage of cases. "Hyperacid" values have been found by very few workers in verified instances of cancer. The conditions under which acid is said to be present are (*a*) in early cancers, (*b*) in small pyloric growths, and (*c*) in cancer originating from a previous ulcer. We shall not discuss the voluminous literature on ulcer-cancer because in the present series it was not possible to prove that peptic ulcer had preceded cancer, although the possibility was considered in a few of the cases.

Practically all the work reported in the literature has been done on gastric contents removed after a test-meal of some sort. Hence there are no data on the important question of the volume of secretion in cancer nor are there any systematic studies of acid values after a powerful stimulus such as is afforded by histamine.

Material and methods

Nineteen cases of cancer of the stomach were studied; most of them were verified at operation or autopsy. The material was selected in so far as a number of patients in the terminal stages, with huge growths and extensive metastases, were not included. Our purpose was to study carefully a small series representing various types of

the disease, rather than to assemble large statistics. On this account, no conclusions can be drawn as to the frequency of anacidity.

All the patients were observed in the hospital. If pyloric obstruction existed, the stomach was carefully washed out for several days before the tests were made. In no case was food taken during the preceding eighteen hours. A small tube was then passed into the stomach and the total secretions were aspirated continuously and collected over successive ten-minute periods (1). After two or more fasting periods histamine (ergamine), 0.1 mgm. per 10 kilos of body-weight, was given subcutaneously and the secretions were collected over three to six more ten-minute periods. No test-meal was introduced into the stomach. The material was studied as to its gross appearance, its amount, the presence of acidity (titratable), the pH and the ferment content. In a few cases chloride, nitrogen and total base were determined. The results, as will be seen below, were correlated with various clinical features such as the size and position of the growth.

Results

The principal data are summarized in Table I, and may be analyzed in detail as follows:

Gross characteristics of the gastric secretions. The most striking feature was the small volume of the gastric secretions (see below). As a rule, they were obviously abnormal in gross appearance. Typical material consisted of more or less tenacious mucoid, grey or brownish fluid. In a number of instances it was frankly bloody, in some slightly blood-tinged. In two cases the fluid was foul; in case 104 it was thin and clear, although no acid was present. In the cases in which there were nearly normal acid values, the appearance of the juice was clear, colorless and in no way remarkable.

Volume of secretion. One of the most striking features of the gastric secretions in these cases was the small volume. In the patients with anacidity the maximum quantity obtained during a ten-minute period was practically never over 10 cc.; as a rule one obtained only 1 to 5 or 6 cc. Furthermore, there was no uniform rise after histamine stimulation and it seemed quite clear that true gastric secretion was entirely or almost entirely in abeyance and that one was obtaining

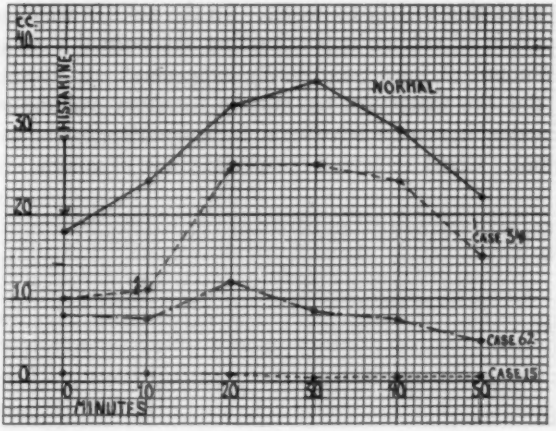

CHART 1. CURVES OF SECRETORY VOLUME FROM CASES OF CANCER OF STOMACH

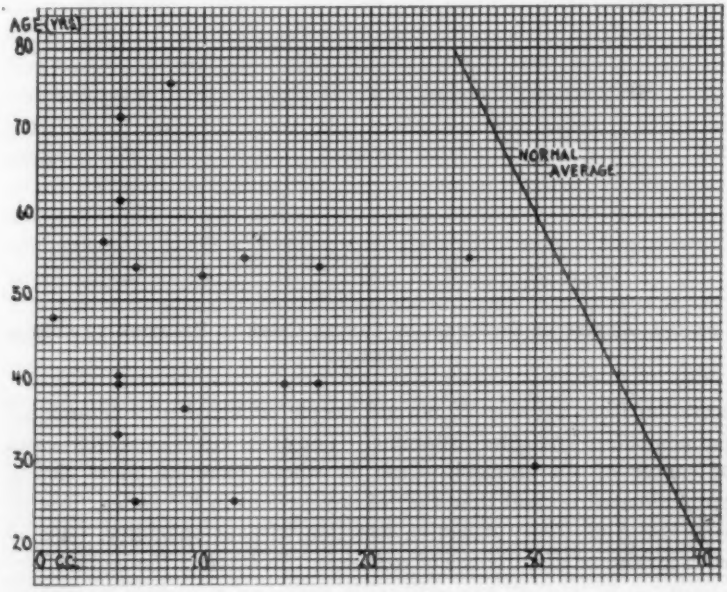

CHART 2. VOLUME OF SECRETION OF CANCER CASES IN RELATION TO NORMAL AVERAGE

material consisting mainly of mucus. In the cases in which acid was present curves of volume approximating the normal were obtained but the amount of juice was usually subnormal. In Cases 34 and 1B only did the maximum ten-minute secretory volume approach a normal value; in no case have we so far encountered volumes greater than normal. Chart 1 shows a composite curve of volumes of gastric

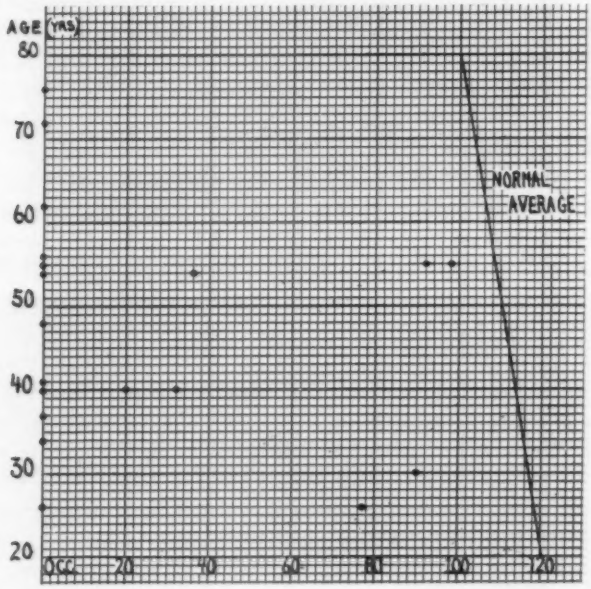

CHART 3. ACIDITY OF SECRETION OF CANCER CASES IN RELATION TO NORMAL AVERAGE

secretion from a group of normal people collected over ten-minute periods before and after histamine. The other curves are from cases of cancer of the stomach—Case 34 whose secretion more closely approximated normal than that of any patient in the series, Case 62 who had a markedly defective secretion without anacidity, Case 15 with maximum disturbance of secretion. In Chart 2 the highest ten-minute yield from all the patients in the series is plotted in relation

to a curve showing the average normal values at various age periods. It is seen that in no instance was the volume of secretion above the normal and in nearly every case it was markedly below. This fact has proved to be a practical diagnostic aid of great value. Given a case which is clinically in doubt, the finding of values above normal practically rules out the presence of cancer as far as our experience up to the present time is concerned. Low values, provided a pyloric obstruction or a mass is present, point almost without exception to cancer.

Acid. The majority of the patients had an "anacidity" of the gastric juice as tested by di-methyl; several had acid in distinctly subnormal concentration, only three (Cases 34, 105, 1B) yielded values approaching normal. In Chart 3 the highest free acid value reached after histamine stimulation in each case is charted in relation to a curve of average acidity obtained from a series of people without gastric disease. As with volumes, acid values above normal average have not yet been encountered by us in patients with cancer. Hence such values would be evidence against cancer in a doubtful case. Low values, on the other hand, may be present in other conditions besides a growth—in gastritis of various kinds. The pH of the gastric juice was tested colorimetrically in some of the cases. Where a complete absence of acid exists the pH reading is usually 6 to 8. In several of the cases (101, 103), even though no test for free acid was obtained with di-methyl, the pH fell in successive specimens after stimulation to a pH of 3 to 5, indicating that traces of acid were being secreted.

Pepsin. Titration of pepsin was done in 5 cases by a method previously described by us (17). No specific diagnostic information was obtained, since the rate of pepsin output varied with the degree of gastric damage as indicated by acid output. It is of interest that some pepsin was still demonstrable in a number of cases in which there was no free acid, a fact recognized by the early observers. Whenever acid was present in appreciable quantity pepsin was also obtained in amounts varying up to normal limits. The actual figures are shown in Table I. One cubic centimeter of gastric juice from a normal stomach at the height of secretion digests at least 15 grams of edestin by our method.

TABLE I

Summary of cases of cancer of stomach

NAME	NUMBER	AGE	SEX	DURATION OF SYMPTOMS	LOCATION OF LESION	SIZE (CM.)	PYLORIC OBSTRUCTION	CHARACTER OF MATERIAL	GREATEST 10-MINUTE SECRETORY VOLUME (CC.)	FREE HCl (HIGHEST)	TOTAL ACID (HIGHEST)	LOWEST pH	PEPSIN CONCENTRATION (MGM. EDESTIN DIGESTED BY 1 CC.)	GREATEST PEPSIN OUTPUT PER 10-MINUTE PERIOD (MGM. EDESTIN DIGESTED)	HISTOLOGICAL VERIFICATION	REMARKS
G.	34	55	M.	7 months	Pylorus	8	Marked	Thin, clear	26	98	112					Gastro-enterostomy. Lived 12 months. Ascites before death
D.	105	55	M.	4 months	Antrum	3	Slight	Clear fluid	12.5	92	106				+	Resection. Died, infection
To.	1B	30	M.	1 year	Pylorus	10	Marked	Clear fluid—blood-tinged	30	90	110				+	Large annular growth—metastases—gastro-enterostomy
V.	1C	26	F.	2 years	Less. Cur.	5	None	Thin, clear	12	77	84					May have begun as ulcer. Lived 6 months. Died, carcinomatosis
H.	6	53	M.	4 months	Pylorus	4	Moderate	Colorless, mucoid	10	36	50				+	Resection of pylorus and gastro-jejunostomy. Lived 6 months. Metastases
F.	62	40	M.	4 months	Pylorus	1	None	Thin, clear, mod. mucus	15	32	47		1,080	15,130	+	Resection. Died peritonitis
A.	207	40	M.	years	Pylorus	10+	Marked	Thin, clear fluid	17	20	44				+	Inoperable growth with metastases. Gastro-enterostomy
W.	15	48	M.	3 months	Pylorus	8	Marked	Opaque, thin, mucoid	1	0					+	Gastro-enterostomy. Gland shows cancer. Lived 8 months
C.	32	37	M.	4 months	Pylorus	3	Marked	Thin, mucoid	9	0		7	157	1,413	+	Excision of growth
S.	51	72	M.	2 months	Body	All but 10 cm. at fundus	None	Grey-brown mucoid, foul	5	0		6	57	285	+	Lived 1 month. Autopsy. Entire stomach except about 10 cm. at fundus is an ulcerated growth
Z.	53	62	M.	5 months	Pylorus and antrum	6	Moderate	Bloody, thin fluid	5	0		7	66	200	+	Possibility of old ulcer. Gastro-enterostomy. Lived 5 months
K.	112	54	M.	3 weeks	Near cardia	5	None	Blood-tinged mucoid	17	0		8				Gland showed adeno-carcinoma
S.	59	40	M.	3 months	Fundus	½ of stomach	None	Turbid, thick fluid, foul	5	0			21	118		Exploratory laparotomy
J.	101	54	M.	2 months	Body	10	None	Turbid, colorless	6	0		4				Lived one month. No operation or autopsy
B.	103	76	M.	3 months	Fundus	"Large"	None	Bloody, mucoid	8	0		3+				
M.	104	26	F.	3 years	Pylorus	8	None	Thin, clear, sticky	6	0		6+			+	Gland shows carcinoma. Gastro-enterostomy
H.	125	40	M.	6 months	Antrum		None	Bloody fluid	5	0						
W.	126	57	M.	3 years	Pylorus and antrum	½ of stomach	Slight	Bloody—mucoid	4	0		8				Question of old ulcer. Gastro-enterostomy
Sh.	1A	34	M.	3 months		10	Slight	Clear fluid	Small	0					+	Huge malignant polypoid growth. Resection

Mucus. There are statements in the literature which suggest that large amounts of mucus may be secreted in cancer of the stomach. In the present series this was not the case. The gastric juice was to be sure often very mucoid, but the total quantity of secretion was so

TABLE II

Chloride, base and nitrogen in gastric juice from cases of cancer of the stomach

10-minute period	Total gastric juice, cc.	Appearance	Chloride		Base		Nitrogen	
			Mgm. per 100 cc.	Total mgm.	Meq./L.	Total Meq.	Mgm. per 100 cc.	Total mgm.
		Case 34						
1	17	Watery fluid—faint bile tinge	514	87.4	71.5	1.21	108	18.4
		Histamine 0.7 mgm.						
2	11	Same	497	54.7	60.2	0.662	97.5	10.7
3	26	Clear	529	137.5	49.5	1.287	73.5	19.1
4	26	Clear	536	139.4	39.4	1.024	54.0	14.0
5	24	Clear	536	127.2	38.3	0.919	58.5	14.0
6	15	Clear	535	80.3	43.0	0.645	77.5	11.6
		Case 32						
1	7	Turbid fluid—some small particles	160	11.2	69	0.483	108.7	7.56
		Histamine 0.7 mgm.						
2	5	Turbid fluid—some small particles	207	10.3	76	0.380	123.6	6.18
3	7.5	Turbid fluid—some small particles	200	15.0	61	0.457	146.3	10.95
4	10.5	Turbid fluid—some small particles	284	29.8	60	0.635	161.3	16.90
5	8	Turbid fluid—some small particles	333	26.6	51	0.408		
6	10	Turbid fluid—some small particles	354	35.4				
		Case 6						
1	10	Mucoid, slightly bile-stained	326	33.3				
		Histamine 0.6 mgm.						
2	6	Colorless mucoid	403	24.2				
3	10	Colorless mucoid	322	32.2				
4	6.5	Colorless mucoid	431	18.0				
5	4.5	Colorless mucoid	473	21.2				

much reduced that one could in no sense speak of a mucorrhoea; in fact the total output of mucus always appeared to be reduced.

Chloride, fixed base, nitrogen. Determinations of these substances were made in two cases (nos. 32, 34), one with a practically normal

secretion, the other with an anacidity. Chlorides were determined in Case 6. The results are shown in Table II. The figures from Case 34 fell within normal limits (18); those from Case 32 corresponded with the data which we have reported in instances of anacidity (19) from a variety of causes, and those from Case 6 were intermediate. There are evidently no specific findings as regards chloride, base and nitrogen in cancer of the stomach.

Relation of size, position and duration of the growth to gastric secretion. There was no definite correlation between the size of the growth and the character of the gastric secretions. Case 34, who yielded a practically normal gastric secretion with a free acid of 98, had a large growth, 8 cm. in diameter, which could not be resected. Case 62, on the other hand, with a small lesion only 1 cm. in diameter, had a free acid of only 32, and Case 32 with a readily removable cancer only 3 cm. in diameter had an anacidity. Further details may be obtained from Table I. The present studies do not support the view that acid is present because the growth is early or small.

All the cases with free acid had lesions at the pylorus, but anacidity occurred with growths located in any part of the stomach.

In one patient (Case 32) with an anacidity we had an opportunity to make a second examination ten months after resection of a pyloric growth. There had been no evidence of recurrence in the stomach, but there was no suggestion of a return of gastric secretion. In Case 207, our first examination, made in July, 1929, at a time when the lesion was so small that it was not definitely demonstrable by X-ray, showed a maximum ten-minute volume of 25 cc. with free acid 15 and total 32. On November 12, when the growth had assumed large proportions, the maximum volume was 17 cc. with free acid 20 and total 44. There had evidently been no deterioration of secretory function in proportion to advance of the disease. Still another case (no. 105) showed on April 25, 1929, a maximum volume of 12.5 cc., free acid 92, total acid 106, and on October 1, 1929, a maximum volume of 23 cc., free acid 96, total acid 106—if anything, an improvement of function. These observations are not in accord with the undocumented statement made so often in the literature that acid decreases as the growth extends.

THE QUESTION OF THE CAUSE OF THE CHANGES OF GASTRIC SECRETION IN CANCER OF THE STOMACH

In the previous section we have described the alterations in the quantity and quality of the gastric secretions which occur in the majority of cases of cancer of the stomach. It remains to discuss the possible causes for these changes in function.

Literature

That the gastric secretions might be altered in instances of advanced ulcerating cancer of the stomach has seemed natural enough to most of the writers who have studied the subject, but it has been more difficult to understand how a small growth, localized perhaps in the submucosa of the pyloric region, could cause an anacidity.

The following explanations have been advanced in the literature to explain defective secretion:

1. Neutralization of gastric juice by duodenal contents.
2. Suppression of gastric secretion by mucus.
3. Injury of the acid-bearing glands of the pylorus by the growth.
4. Interference with gastric nerves by the growth.
5. Neutralization (or inhibition) of gastric juice by alkaline products of the growth.
6. Chloride starvation.
7. Gastritis associated with the growth.

Of these theories the one which has been most widely held is that a gastritis associated with the growth is responsible for changes in the secretions. The first extensive study of the question was that of Lebert (20) (1878), who found in 41 out of 56 cases an extensive gastritis even at a distance from the growth. Rosenheim (21) ten years later investigated the question very carefully. Extensive gastritis was found in fourteen stomachs with cancer in which anacidity had been present during life. Another case of cancer (verified) with normal acid showed no gastritis at autopsy. Rosenheim expressed the opinion that the growth itself had nothing to do with the alteration in the secretions but that the changes, if present, were due to gastritis. The latter, however, he implies is in some way caused by the growth. Subsequently Stienon (22), Miehe (23), Fischel (24), Ewald (25),

Hammerschlag (26), Boekelmann (27), Einhorn (28), Riegel (29), Cohnheim (30), Matti (31), Steinberg (32), Geissendorfer (33) and others studied the question; all agreed as to the frequency of diffuse gastritis or areas of gastritis in stomachs the seat of cancer, and felt that the changes in secretion are due to this rather than to the growth itself. Fischl's paper gives one of the best early descriptions of histological changes which are classified as catarrhal, interstitial and atrophic. Riegel was one of the first to stress the view that the gastritis was caused by the cancer, although no explanation is given of how this effect is brought about. Practically all subsequent writers have agreed with this interpretation, although Rosenheim pointed out that the changes were similar to those found in stomachs the seat of gastritis but not of cancer. Mathieu (34) was practically the only one of the earlier writers who expressed the opposite point of view, that a pre-existing gastritis predisposed to the later development of cancer, until Konjetzny and Saltzman, in 1913, produced very positive evidence on the pathological side by demonstrating histologically transitions from gastritis to actual cancer (35). Hurst (36) has recently strongly supported this view on clinical grounds. Reisner (37) minimized the importance of the gastritis and without any very conclusive evidence stressed the view that anacidity in cancer of the stomach was due to chloride starvation and to alkaline products of the growth. His views influenced a number of successive writers. Brown (38) in a recent textbook summary states that "practically every gastric cancer after a certain length of time leads to chronic gastritis, and often to atrophic gastritis with achylia."

The various theories may now be discussed in the light of our own observations.

1. Neutralization of gastric juice by duodenal contents. With respect to this theory, as well as to some of those discussed below, the estimation of the volume of the gastric juice has been of value. In all the cases with anacidity the volumes (see Table I) were extremely low; indeed in some instances practically no material was obtained on aspiration (Case 15). Had there been a regurgitation of duodenal juice the volumes obviously would have been considerable. Further evidence against regurgitation is the absence of bile in the gastric contents of our cases. Finally, the low chloride in Cases 6 and 32 can not be explained by simple neutralization.

2. Suppression of gastric secretion by mucus. Here again the small volumes of juice in the cancer cases with anacidity would rule out a mere neutralization of a normal acid output by excessive secretion of mucus, nor is there any evidence of the presence of any great amount of this material.

3. Injury of "acid-bearing glands of the pylorus" by the growth. This theory would seen untenable when one considers that even large lesions of the pylorus, if not malignant, are not associated with absence of gastric acid. We have repeatedly found very high values for both acid and volume in cases of huge pyloric ulcer. Furthermore, normal values may be obtained with quite large pyloric cancers (Case 34) whereas anacidity may exist with small ones (Case 32). Finally, anacidity occurs equally with growths at the cardiac end of the stomach, and above all *acid-producing cells do not exist at the pylorus* (39).

4. Interference by the growth with the gastric nerves. Observations with atropine and histamine on normal people make this theory also untenable. Large doses of atropin may practically abolish gastric secretion, but the small amount of juice obtained, if histamine is now given, shows no reduction in acidity but usually an increase (40). It seems unreasonable to believe that a small growth at the pylorus could cause a greater vagal paralysis than full doses of atropin.

5. Neutralization or inhibition of secretion by alkaline products of the cancer. This theory fails entirely to account for the small volumes of juice found in cancer cases and it would be difficult to accept it in the case of small submucous growth as in Case 62.

6. General chloride depletion of the body. This theory—advanced many years ago—is obviously inadequate in the light of modern knowledge; witness patients with marked depletion of blood chloride from vomiting associated with benign pyloric obstructions who still pour out large amounts of very acid juice.

7. Gastritis associated with the growth. The undoubted fact of the presence of a diffuse gastritis in cases of cancer of the stomach with anacidity has been discussed above. One can hardly evade the supposition that such a gastritis may be the direct cause of the defective secretion and the point at issue is rather the causal relation of the growth to the gastritis. As we pointed out in reviewing the literature,

most observers have concluded or assumed that the growth *produces* the gastritis, which in turn is supposed to lead to the deficient secretion. It seems to us, however, that all the evidence points the other way and we must agree with Mathieu's long neglected view that gastritis precedes the growth, and that cancer is prone to occur in stomachs already the seat of chronic changes. The following arguments may be brought forward:

First of all, the assumption that a small cancer, perhaps submucous, can produce a gastritis is entirely gratuitous. Benign ulcerations with stasis existing for long periods of time fail to cause gastritis of the type found with cancer and one would have to assume in the former case some purely hypothetical poison which would produce the injury. Secondly, if the growth produced the gastritis, one would expect less change in the early stages of the cancer and would expect to find a progressive impairment of gastric function as the disease advances. While this is stated in the literature to occur, we have been unable to find any specific record of findings and are disposed to question such a sequence of events. In our own cases the presence or absence of acid could by no means be related to the extent or duration of the growth except perhaps in such terminal cases as those in which almost the whole mucosa was destroyed by a sloughing growth (see previous section). Finally the gastritis in cancer cases differs in no way as regards the secretory findings from that found in many people who have no cancer. This matter will be discussed more fully in another paper.

SUMMARY

Most cases of cancer of the stomach show a deficient gastric juice as evidenced especially by abnormally small volumes of secretion with low acidity or with absence of acid. A small proportion of the cases have secretory findings within normal limits. We have so far encountered no instance with acid or volume of secretion definitely above the average. The diagnostic implications are indicated.

All evidence points away from the occurrence of cancer in the previously normal stomach, although this may occur in a very small percentage of cases. Cancer appears to arise almost always on the basis of an already existing lesion, usually a chronic gastritis, less frequently a peptic ulcer.

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THE FORMATION OF EPITHELIOID CELLS AND GIANT CELLS IN THE SUBCUTANEOUS TISSUES FOLLOWING THE INTRODUCTION OF PHOSPHORUS IN OIL[1,2]

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In the course of a series of experiments in which olive oil containing small amounts of yellow phosphorus was injected subcutaneously, examination of the tissues at the site of injection revealed cellular changes which were of considerable interest. These observations have an important bearing upon the nature of the stimulus involved in the formation of the so-called epithelioid cell as well as upon the foreign-body reaction in general. It is in connection with the former relationship that we are particularly concerned here.

The observations of Cunningham, Sabin, Sugiyama and Kindwall (1) gave us a definition of the principal cell concerned in the reactions of the tissues in tuberculosis in terms of individual cell morphology, and thus extended our basic knowledge of the pathology of this disease. They based this definition upon certain characteristics of the living cell. Previously, the epithelioid cell could be specifically identified only when found in numbers either in definite tubercles or in generalized tuberculous tissue. Due to the criteria established by the observers mentioned above, the individual epithelioid cell became a distinct entity, capable of specific identification even when entirely dissociated from the lesion of which it formed a part. Their morphological studies also indicated that this cell, as seen in the living state, is marked especially by a diminished capacity to phagocytize foreign materials. The suggestion was made that tubercle bacilli were ingested by monocytes and that the subsequent reactions of these cells to the bacilli included some injury which resulted in a progressive

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diminution in phagocytic capacity, in a lessened ability to digest included materials, and, finally, in the death of the cell with liberation of the bacilli contained within it. It was also suggested that the bacilli often increased in number within the cells while these morphological changes were taking place.

It is obvious that, if the above interpretation is correct, the production of epithelioid cells in tuberculosis is initiated from within the cells by the presence of tubercle bacilli. Recently Sabin and Doan (2) have shown that similar cells in great numbers can be produced by means of the phosphatid fraction obtained from tubercle bacilli by chemical extraction. Still later Sabin, Doan and Forkner (3) have shown that a dextro-rotary fatty acid obtained from the same source will produce these cells in even greater amounts. However, their studies do not indicate whether these substances exert their actions from within the monocyte, or whether they act upon it from the outside.

In the work referred to above (1) the conclusion was reached that the epithelioid cell was a specific derivative of one type of phagocytic mononuclear cell, the monocyte, which occurs quite generally in connective tissue. In these studies, however, it was pointed out that there was a widespread active formation of new monocytes from their parent cell (the reticular cell).

In the experiments reported here it was found that, when a solution of phosphorus in oil was introduced subcutaneously in the guinea pig, large numbers of typical epithelioid cells were produced. In addition, typical Langhans giant cells were often found, and great numbers of cells whose nature could not be determined further than that they were probably epithelioid cells which had undergone degeneration. This conclusion was based on their enormous content of fine fatty droplets (see Fig. 10). We do not feel that, in these observations, we have definite information concerning the etiology of epithelioid and giant cells. We are specifically concerned with pointing out the fact that typical epithelioid and giant cells, wholly indistinguishable from those found in tuberculous reactions, can be produced in large numbers in the subcutaneous tissues of the guinea-pig following the introduction of yellow phosphorus in a menstruum of olive oil.

TECHNIQUE

Guinea-pigs were used for these experiments. One-half to one cubic centimeter of olive oil containing one milligram of yellow phosphorus in each cubic centimeter was injected subcutaneously. After various intervals of time the area was incised and scrapings of the fresh tissue were studied supravitally. Also, very small films of tissue were removed and spread on slides for study. These examinations were made on slides previously coated with neutral red. Where the tissues were not sufficienctly moist, a drop of serum was added in order to obtain a preparation with sufficient fluid to insure solution of the dye.

OBSERVATIONS

Plate 1 shows very graphically the range of epithelioid and giant cells obtained in these experiments. We have not included drawings of any of the other types of cells seen. In these illustrations vacuoles stained with neutral red are shown in black, while fat droplets appear as small circles. The cytoplasm was granular. This is indicated in the drawings by fine stippling.

In a few instances granulocytes were seen. The vast majority of the vitally-stained cells were monocytes, epithelioid cells and clasmatocytes. Giant cells were also frequently found. Early in the reactions large numbers of both clasmatocytes and monocytes were always found. Many of these cells contained a few fat droplets. Various amounts of intracellular fat were seen at every stage. Many cells of various sizes were seen whose cytoplasm was filled with fat droplets. One such cell is shown in Figure 10. Typical monocytes with no increase in neutral red, but with a few scattered droplets of fat about the periphery, were routinely found in all the preparations but were in the greatest proportion in those made from three to five days after the injection of the phosphorus and oil.

Beginning about the fourth or fifth day, typical epithelioid cells began to appear. Cells of this type are shown in Figures 1, 2 and 3. The cell shown in Figure 3 is somewhat larger than the cells ordinarily found at this period, but is included with this type of cell because of the relatively small size of the rosette. The larger expanse of cyto-

plasm without increase in size of the rosette probably indicates that this cell was growing rapidly. Cells of this type were often seen between the fourth and seventh days. By the eighth day fully formed typical epithelioid cells (Figs. 4, 5, 6) were seen interspersed with great numbers of smaller cells filled with fat and evidently dying or dead. The epithelioid cells on the fourth and fifth days often contained a few droplets of fat, while later they became progressively more loaded until eventually their cytoplasm was completely filled with these droplets. The nucleus was often so buried beneath these droplets that it became entirely lost to view.

The changes in the course of the formation of the typical epithelioid cells were gradual and continuous and can not be divided into definite periods. These changes consisted in the formation of the rosette of fine neutral red vacuoles and the accumulation of fatty droplets. A preponderance of epithelioid cells was usually present by the seventh or eighth day. Following this, however, the relative numbers of the various stages in their development and disintegration seemed to depend upon many factors. Among these may be enumerated the relationship of the cells in question to the mass of the oil at the point of injection, the number of injections, and the amount of inflammatory reaction which had taken place about the area of infiltration. It was clear, however, that many of the cells which were in contact with the oil went through a rather definite cycle from monocytes to epithelioid cells, to cells filled with fat and to eventual death. Many of the cells seen in the earlier preparations were loaded with fat. These had probably not undergone the specific changes in the vacuolar content involved in the production of epithelioid cells. Others showed the typical vacuolar arrangement of epithelioid cells, but seemed to have become loaded with fat before the development of the vacuoles had progressed very far. Such a cell is shown in Figure 5. Cells were found in which nuclear division had taken place, and in which fat had accumulated rapidly and the cell development stopped at this point (shown in Figs. 7, 8 and 10). Others were seen in which nuclear division continued without division of the cytoplasm and therefore with the eventual production of typical giant cells as shown in Figure 9.

In other words, the course of the production of the epithelioid cells was marked first by the development of the fine vacuoles which stained with neutral red. These fine vacuoles we have assumed to be characteristic of this type of cell. This was followed by the accumulation of fat, and the progressive nuclear division without division of the cytoplasm, which resulted in the formation of the typical rosette giant cell with all of the characteristics of those found in tuberculous tissue. In many instances the epithelioid cells became filled with fat before the process of nuclear division had begun. The large number of cells filled with fine droplets of fat but having no vacuoles staining with neutral red were assumed to be epithelioid cells degenerating in this manner.

CONCLUSIONS

The subcutaneous injection of guinea-pigs with olive oil containing yellow phosphorus caused the production of large numbers of typical epithelioid cells and giant cells, which were indistinguishable from those found in tuberculous lesions.

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PLATE 1

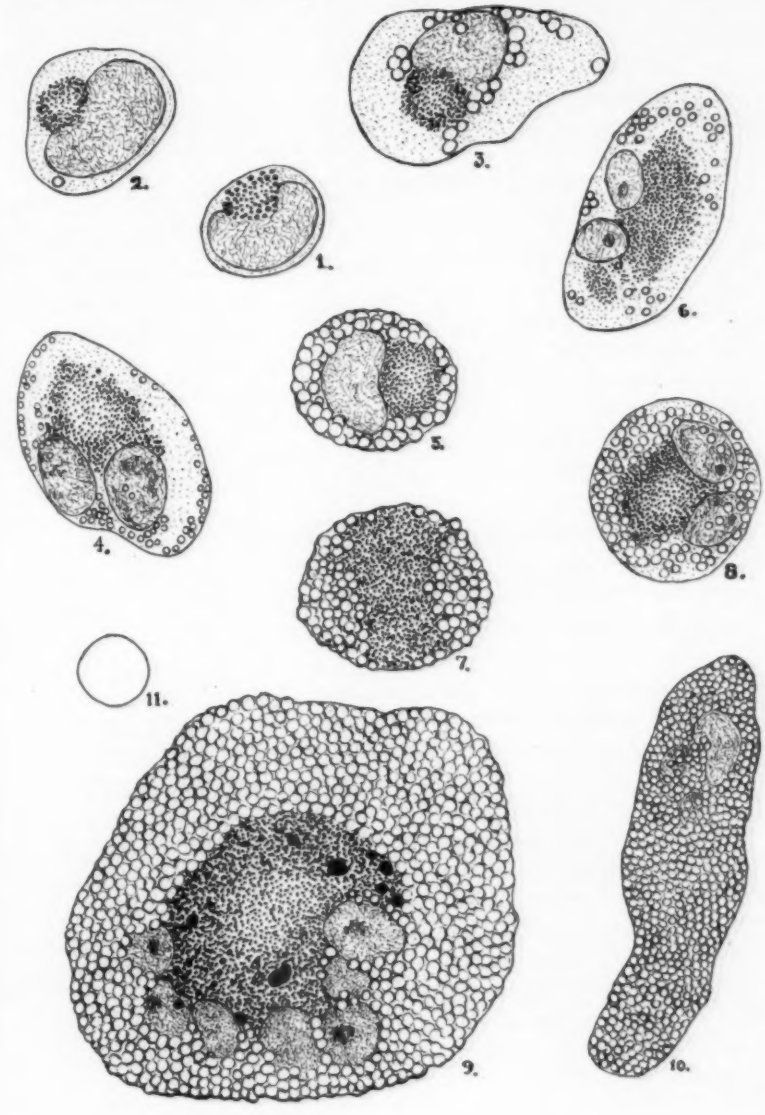
Vacuoles stained with neutral red are shown in black. Fat droplets are represented by circles. The granular cytoplasm is indicated by fine stippling.

FIGS. 1, 2 AND 3. Epithelioid cells from scrapings of the 4th and 5th days following injection.

FIGS. 4, 5, 6, 7 AND 8. Epithelioid cells from scrapings of the 8th and 9th days.

FIG. 9. Giant cell from scrapings of the 9th day.

FIG. 10. Dead cell from the scrapings of the 9th day.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PSYCHOGALVANIC REACTION TO PAINFUL STIMULI IN HYPNOTIC AND HYSTERICAL ANESTHESIA[1]

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In all types of cutaneous anesthesia and analgesia some variety of dissociation takes place, since the stimuli are not followed by the accustomed responses. In the anesthesia and analgesia produced by anatomic lesions and by toxins, the interference with the production or the passage of the nervous impulse offers a relatively simple explanation of the dissociation. In the anesthesia and analgesia which appear in hypnosis and in hysteria, some variety of dissociation must take place, also. The stimulus fails to produce the accustomed reaction, *viz.*, a change in facial expression and bodily attitude and a report by the subject that he knows that the stimulus has been given. Evidently the dissociation does involve the psychobiologic level of integration. Whether such a dissociation involves changes at lower levels of integration, *e.g.*, the physiologic, constitutes an unsolved problem.

One of the most sensitive of the indicators of a change at the physiologic level is the psychogalvanic reflex, which expresses the slight variations in the electrical state of the skin (probably based on the action currents of the sweat glands).

There is no consensus of opinion on the question of whether the psychogalvanic reflex is called forth by the stimulation of anesthetic areas in hypnosis and hysteria. With regard to hypnosis: Moravcsik (1) in one case, and Georgi (2) in three cases, found that stimulation of an area which was anesthetic in hypnosis produced no psychogalvanic response; Peiper (3), Prideaux (4), in four cases, and Prince and Peterson (5), in one case, obtained the opposite results, *i.e.*, they found that stimulation of the anesthetic area gave normal psychogalvanic responses. With regard to hysteria: Veraguth (6), and

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Prideaux (4), found that stimulation of anesthetic areas in hysterical patients gave normal psychogalvanic responses; Gregor (7), obtained variable results.

EXPERIMENTAL RESULTS

The present records were obtained by photographing the deflections of a string galvanometer. The wires leading to the galvanometer were attached to non-polarizable electrodes (zinc discs plus a kaolin-zinc sulphate paste) which, in turn, were attached to the palms and backs of the hands of the subject. (Apparatus described by Richter (8)). Before each experiment the string of the galvanometer was so standardized (without the subject in circuit) that the introduction into the circuit of one millivolt corresponded to 10 mm. deflection of the shadow of the galvanometer string on the scale of the camera. Then, with the individual in circuit, the skin resistance was measured by recording the number of millivolts necessary to deflect the string 10 mm. If the skin resistance was high, the skin immediately beneath the electrode was punctured, in order to reduce the resistance to the proper level for psychogalvanic records. Before the psychogalvanic record was taken, the string was so restandardized that the introduction of 10 millivolts caused a deflection of 25 mm. Psychogalvanic records were taken with the back and palm of one hand in circuit with the galvanometer.

While the psychogalvanic record was being taken, no external current was introduced into the circuit, and the fluctuations of the galvanometer string resulted entirely from an electromotive force originating in the subject.

In my experience, it is rarely possible to be certain of definite anesthesia during hypnosis. Varying degrees of hypoesthesia can be obtained by suggestion with some frequency, but unmistakable anesthesia is rare. In the course of an investigation on the electrical skin resistance during hypnosis, there was one hysterical subject (S) in whom the hypnosis was very deep and in whom a striking degree of anesthesia was obtained. There was no anesthesia present except as the result of a suggestion during hypnosis. It was possible to stick a sterile venipuncture needle through the patient's skin, when her eyes were closed, without evoking any observable reaction, and

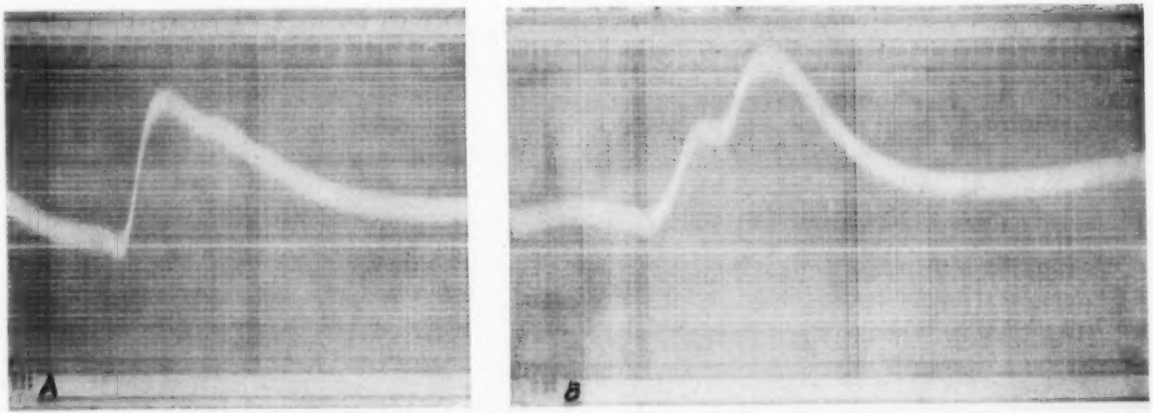

CHART 1. HYSTERICAL PATIENT (S) DURING HYPNOSIS

No anesthesia present except as result of suggestion. Skin punctured by needle at moment indicated by signal marker. Figure A shows the response before anesthesia was suggested. Figure B shows the response after anesthesia was suggested. Time record indicated in seconds.

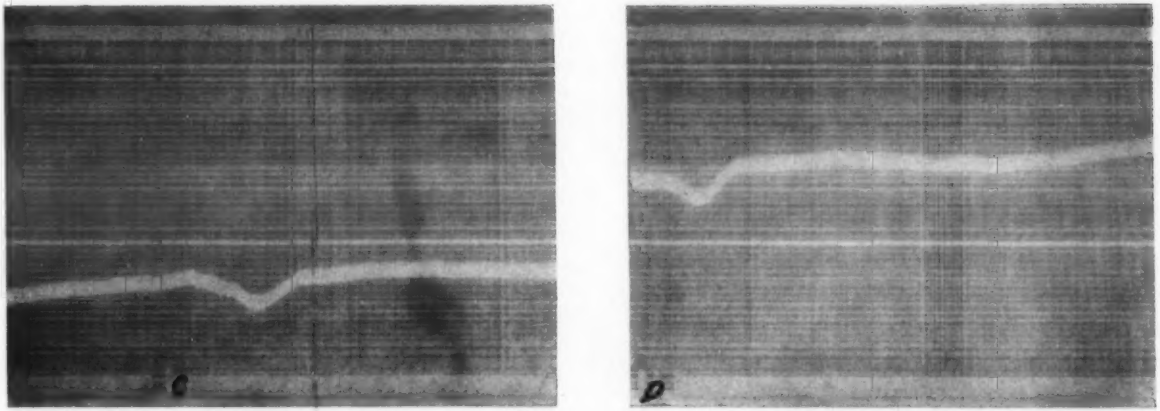

CHART 2. PATIENT S, DURING ANOTHER HYPNOSIS

Skin punctured by needle at moment indicated by signal marker. Figure C shows the response before anesthesia was suggested. Figure D shows the response after anesthesia was suggested.

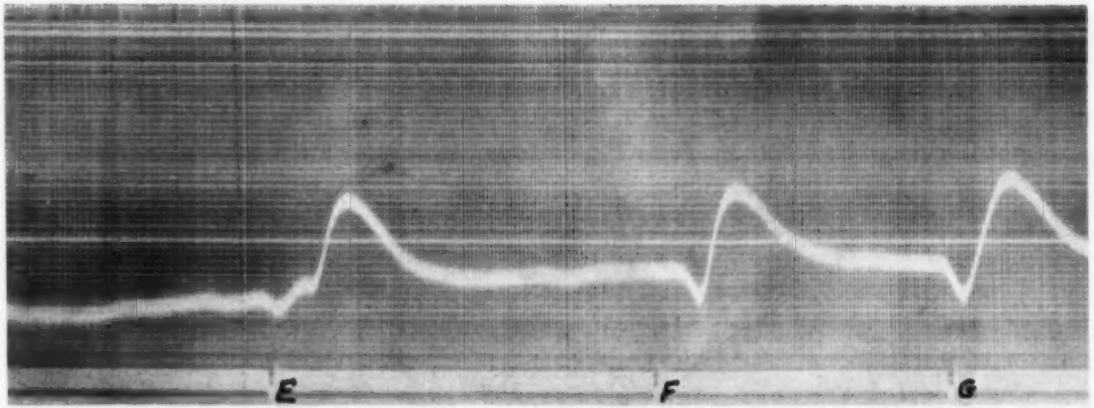

CHART 3. PATIENT M

Hysterical anesthesia. Waking state with eyes closed. Skin punctured by needle at moments indicated by signal marker (E, F, and G).

according to the patient's report, without her being aware of the procedure. The experiment was performed on three separate days and in each instance psychogalvanic responses were obtained which were almost identical with those obtained before the anesthesia was suggested, and in which the patient had shown the facial expression of pain and reported the perception of sharp pain.

The experiments were performed in this way. After the patient seemed deeply hypnotized, the physician continued with the usual suggestions for increased relaxation and deeper sleep. While he talked, he suddenly stuck the needle through the skin of the patient's arm. She gasped, pulled her arm away (several times upsetting the electrode stand) and contracted her facial muscles as if in pain. She was asked "Did you feel anything?", and she said "Yes, it hurt." Then the physician continued with suggestions for deeper sleep and with therapeutic suggestions, for ten to fifteen minutes. Then he said "Now you have lost all feeling in your right arm. If something touches it, you won't be able to feel it at all." Then while the physician said "You're falling deeper asleep all the time," the needle was stuck through the skin of the patient's arm. She did not move, and her facial expression did not change. Then she was asked "Did you feel anything?" and she answered "No."

Examples of the responses obtained are shown in Charts 1 and 2.

The above experiments were performed during the hypnotic state on a hysterical patient (S) who had no areas of anesthesia except as the result of suggestion during hypnosis. Other experiments were performed on another patient (M) who suffers from a persistent anesthesia of her arms and legs during the waking state (*i.e.*, from hysterical anesthesia). When her eyes were closed (during the waking state) it was possible to stick a venipuncture needle through her skin without producing any observable reaction and, according to the patient's report, without awareness of the procedure. Marked psychogalvanic responses were obtained each time the needle punctured the skin, as shown in Chart 3.

In the above experiments the subjects were stuck with the needle without being told that it was to be done. The responses were not the result of the expectation of painful stimuli, nor were they responses to hallucinations of painful stimuli. Each was the direct response to the stimulus itself.

Another type of experiment was performed, which is less directly connected with the problem of anesthesia in hypnosis and hysteria but is of importance in the general problem of the psychogalvanic response. It was found that psychogalvanic responses are associated with hallucinations (of various modalities of sensation) produced by suggestion during hypnosis. For example, when the patient S was deeply hypnotized, it was found repeatedly that a marked psychogalvanic response could be obtained when the painful stimulus was not given, but the patient was told, "Now you can feel the needle

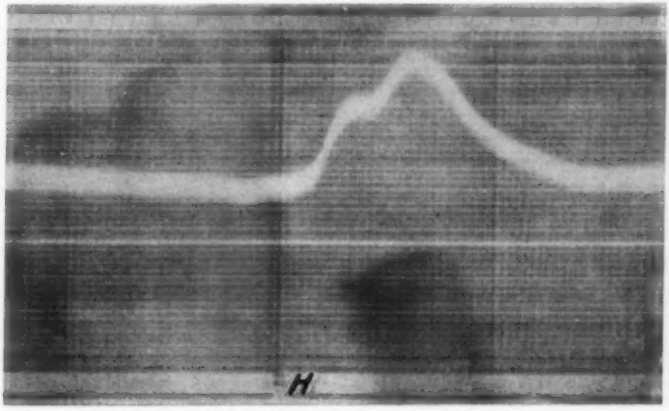

CHART 4. PATIENT S

Hypnotic state without anesthesia. Hallucination of painful stimulus suggested at H. Chart 1 and Chart 4 were taken during the same period of hypnosis.

being stuck in your arm." Her facial expression and bodily movement were those of a person in pain and she reported the perception of sharp pain. Examples of the psychogalvanic responses obtained are shown in Chart 4.

DISCUSSION

Too few cases have been studied adequately to permit generalization, but the observations presented above offer clear evidence in support of the statement that painful stimulation of anesthetic areas

in hypnosis and in hysteria produce psychogalvanic responses. Evidently the dissociation that takes place does not dissociate the stimulus from the psychogalvanic response. The stimulus is dissociated from the usual overt reaction and from the report of the perception of pain, but is still associated with the psychogalvanic response.

It is conceivable that in some cases of hysterical and hypnotic anesthesia there might be a dissociation between stimulus and

TABLE I

SETTING AND STIMULUS			RESPONSE		
"State"	Type of anesthesia	Stimulus	Overt response	Report of perception of pain	Psychogalvanic response
Hypnosis	None	Stuck with needle	Present	Present	Present
Hypnosis	Produced by suggestion, *i.e.*, hypnotic anesthesia	Stuck with needle	Absent	Absent	Present
Waking state	Present without suggestion, *i.e.*, hysterical anesthesia	Stuck with needle	Absent	Absent	Present
Hypnosis	None	Hallucination of being stuck with needle	Present	Present	Present

psychogalvanic response. No clear evidence of such a case has been offered. It might be added that the hypnosis in our case S was regarded as very "deep" by several experienced observers.

SUMMARY

The psychogalvanic response was present (1) when a painful stimulus, given during the hypnotic state without anesthesia (in a hysterical patient), produced overt responses and a report of per-

ception of pain; (2) when a painful stimulus, given during the hypnotic state in an area of anesthesia produced by suggestion (in a hysterical patient), produced no overt responses and no report of perception of pain; (3) when a painful stimulus, given during the waking state to a patient with hysterical anesthesia, produced no overt responses and no report of the perception of pain; and (4) when the hallucination of a painful stimulus, suggested during the hypnotic state, produced overt responses and the report of the perception of pain.

Table I represents the above facts.

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